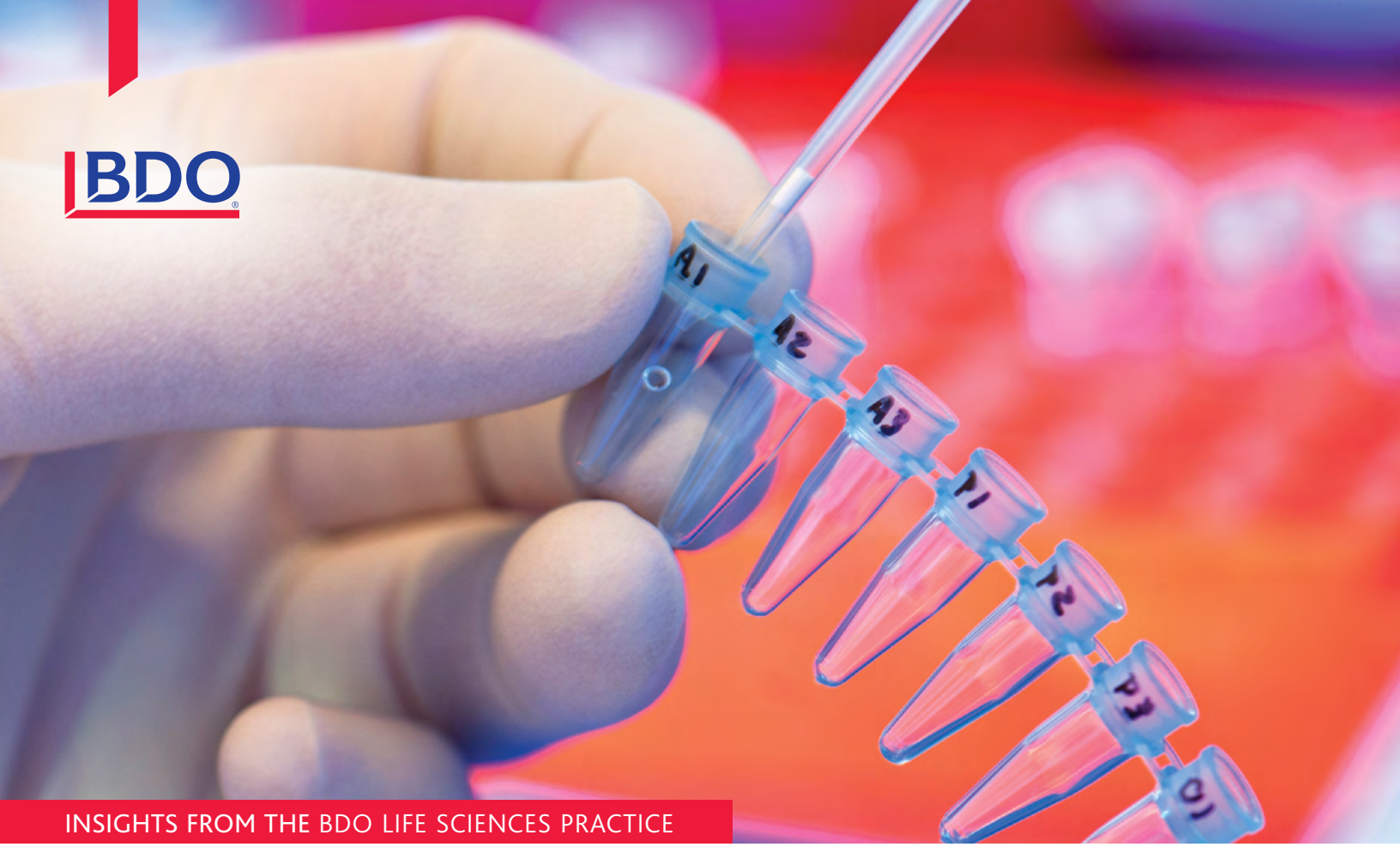

INSIGHTS FROM THE BDO LIFE SCIENCES PRACTICE

THE CELL AND GENE THERAPY TOOLBOX

New treatments create demand for fast-tracking production, approvals process

By Denis Boyle, Ph.D.

There is nothing like dramatic cures of historically fatal conditions to generate widespread medical and investment interest. Global awareness of new cell and gene therapy successes, approaches that directly intervene in the genome of living cells, is putting pressure on innovators and regulators to bring therapies to market as fast as possible. This is demanding new ways to reliably supply therapies to clinics, create novel testing strategies and is forcing proactive company-regulatory collaborations in many countries. Much of the challenge to deliver on these demands rests on the technology developers and their ability to innovate and collaborate. Let's look at the CMC issues associated with three of the hottest areas and some of the challenges associated within each.

THE CHALLENGES AND OPPORTUNITIES THAT ARE FACING CELL THERAPY

The most familiar new cell therapy is the use of a patient's own blood cells (autologous) that are genetically altered outside the body using viruses to create chimeric antigen receptor T cells, or CAR-T cells. These modified cells are returned to the patient where they recognize and kill specific cancer cells. Also, allogeneic approaches are being explored to develop universal cell therapies from selected cell donors. This approach involves using gene editing technologies. However, unintended off-target effects indicate these efforts have a way to go before being commercially feasible.

The biggest challenge facing cell therapy developers is proving lot to lot consistency. Identifying analytical methods for appropriate biomarkers and other quality attributes for incoming patient cells and final product are among the challenges. For example, knowing the amount of the transferred gene and the content variability of the viral containers (capsids) to define final T cell potency are two central issues. In addition, demonstrating the removal of process impurities for safety, is required to establish the minimum package for clinical production.

Quickly establishing an analytical testing program is an enormous company advantage because lot comparability studies occur earlier in development than we've typically seen for recombinant

proteins. Ensuring that reference materials are retained from pre-clinical and early clinical lots for subsequent comparability during characterization, release, and stability studies becomes even more important for these modalities as specifications evolve with process knowledge. For these fast-moving programs, a well-defined analytical testing program will also pay dividends during late stage studies, such as process characterization and validation, to leverage fundamental process understanding into well executed study plans and protocols.

NAVIGATING COMPLEXITY AND THE HURDLES TO GENE EDITING

Enzyme formulations (CRISPR/cas9, TALEN) to add or delete genes directly in somatic cells are in clinical trials and are even more complex to manage. They can have up to three unique active drug formulations and 12 cell banks per product, along with the same safety, potency, identity and dose concerns as cell therapies. Unwanted off-target issues must also be evaluated genome-wide by dose level studies in non-target tissues, i.e., all tissues and organs that are not targeted therapeutically. These off-target tests then become part of routine characterization and release testing. These gene editing programs herald obvious advantages for disease treatment once these development hurdles are overcome.

CREATING PERSONALIZED NEO-ANTIGEN CANCER VACCINES

Training the body's own immune system to find and kill cancer cells is not a new idea but has not been shown to be effective against enough cancer types. The main reason for this is that cancer cells often show molecular differences amongst themselves, so the best targets are often missed. The newest approach is the design of personalized vaccines using a patient's own cancer cells to treat the exact form of cell type encountered. This approach has been proven effective in over **150 trials to date**.

Personalized vaccines are generated through the selection and synthesis of the best antigenic mix of defective protein fragments and/or synthetic peptides isolated from the cell surface of a patient's own cancer cells. These formulations may also contain plasmids, mRNA, antibodies and novel adjuvants and nanoparticles. Because a cancer patient's genome has between 100-1000 non-self-mutations, it's not possible to empirically synthesize each one. Screening for the best patient antigens is necessary because often only a few of the thousands present may be effective.

To treat patients quickly, screening of their cancer antigen mixtures is done by measuring the response of T cells and toll-like receptor recognition signals to normal antigens in the lab. Typically, high throughput bioinformatics machine learning tools and patient data are employed for this screening. Eventually regulators will require validation of the algorithm software at later stages of clinical trial development as antigens become more defined as part of an efficacious product.

CMC CHALLENGES AND THE PROMISE OF CURES VERSUS TREATMENTS

With limited product knowledge and resources, cell and gene therapy product development has advanced by prioritizing the toolbox associated CMC challenges. Each of these technologies requires a different manufacturing process. Therefore, a first concern is to define manufacturing process and productivity to predict demand and identify capacity. Companies should also start planning for manufacturing based on scale changes as process development evolves. Focusing as early as possible on your analytical package will enable the developers to monitor product attributes as the manufacturing process matures. Also, be ready to communicate with regulators during the development pathway. Companies and regulators need to learn from each other. These CMC challenges have been daunting, but the promise of a cure versus merely treating a disease continues to move new cell and gene therapies forward. The story remains one of frenetic activity but continued excitement.

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CONTACT

LANCE MINOR
Principal
301-354-0711 / lminor@bdo.com

TODD BERRY
Assurance Partner and National Co-Leader, BDO Life Sciences
617-239-4125 / tberry@bdo.com

DENIS BOYLE
Director
339-927-6595 / dboyle@bdo.com

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